MH-Related Diseases

Who Really Needs a Non-triggering Technique?

Ron Litman

litmanr@email.chop.edu

Disclosures.....

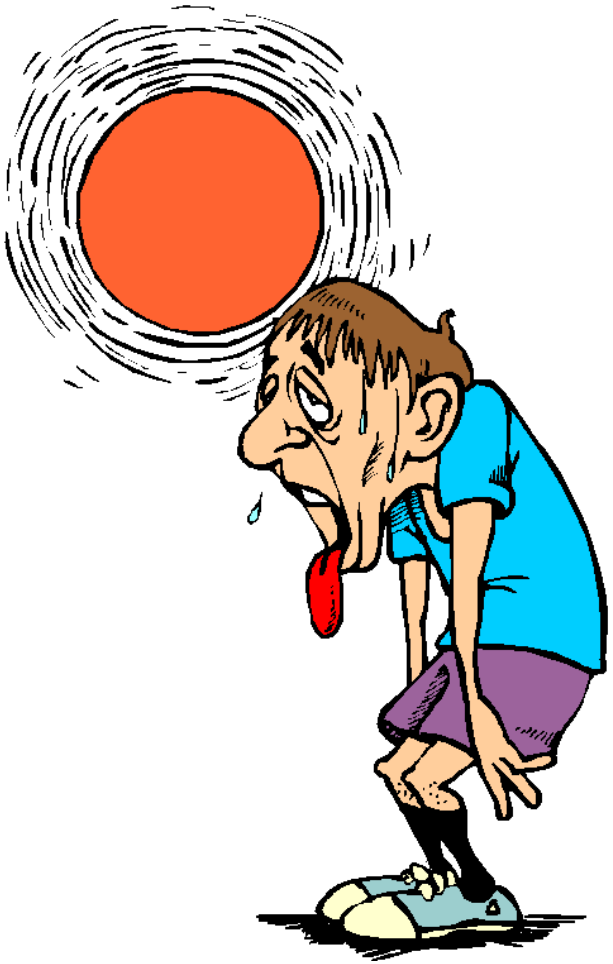
Disclosures…..

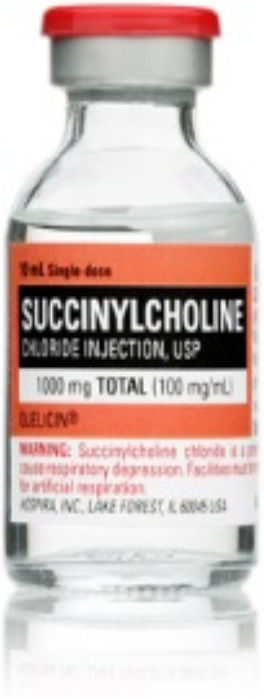
ISMP
INSTITUTE FOR SAFE MEDICATION PRACTICES

Lecture Overview

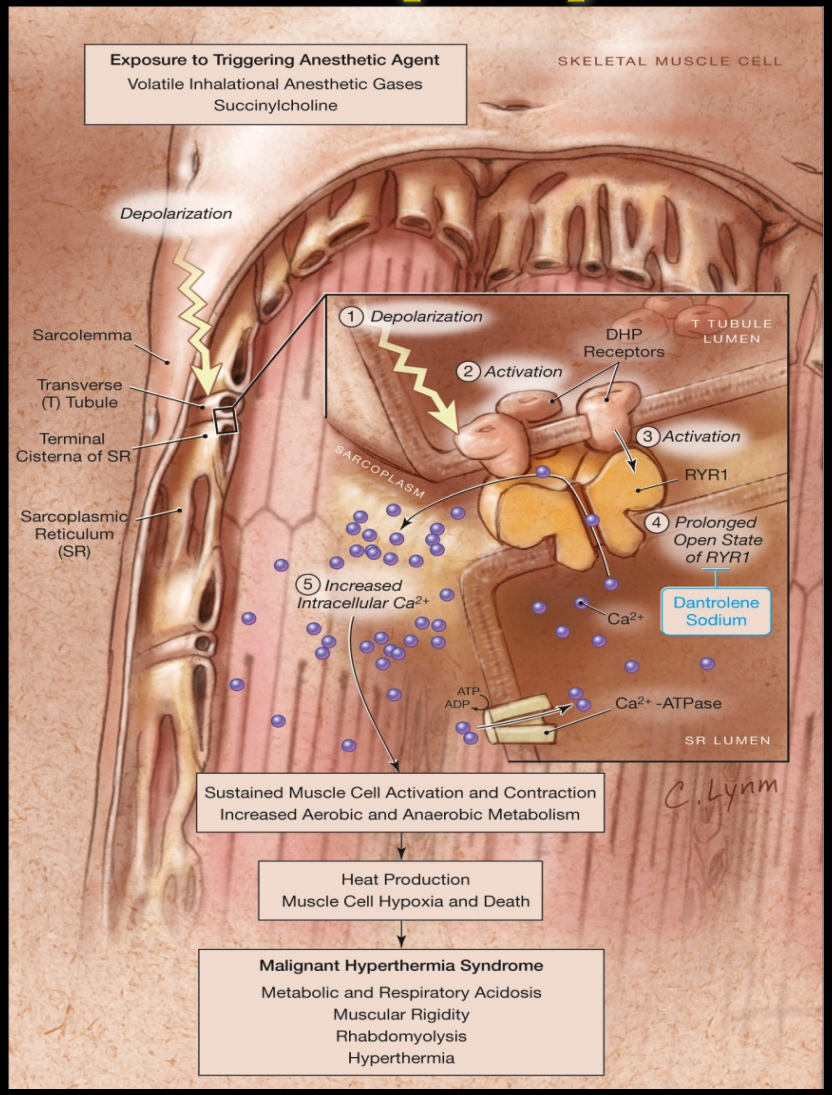
- ✓ *SHORT MH REVIEW*
- ✓ *WHO REALLY NEEDS A NON-TRIGGERING TECHNIQUE?*
- ✓ DIAGNOSTIC TESTING

Important MH Principles

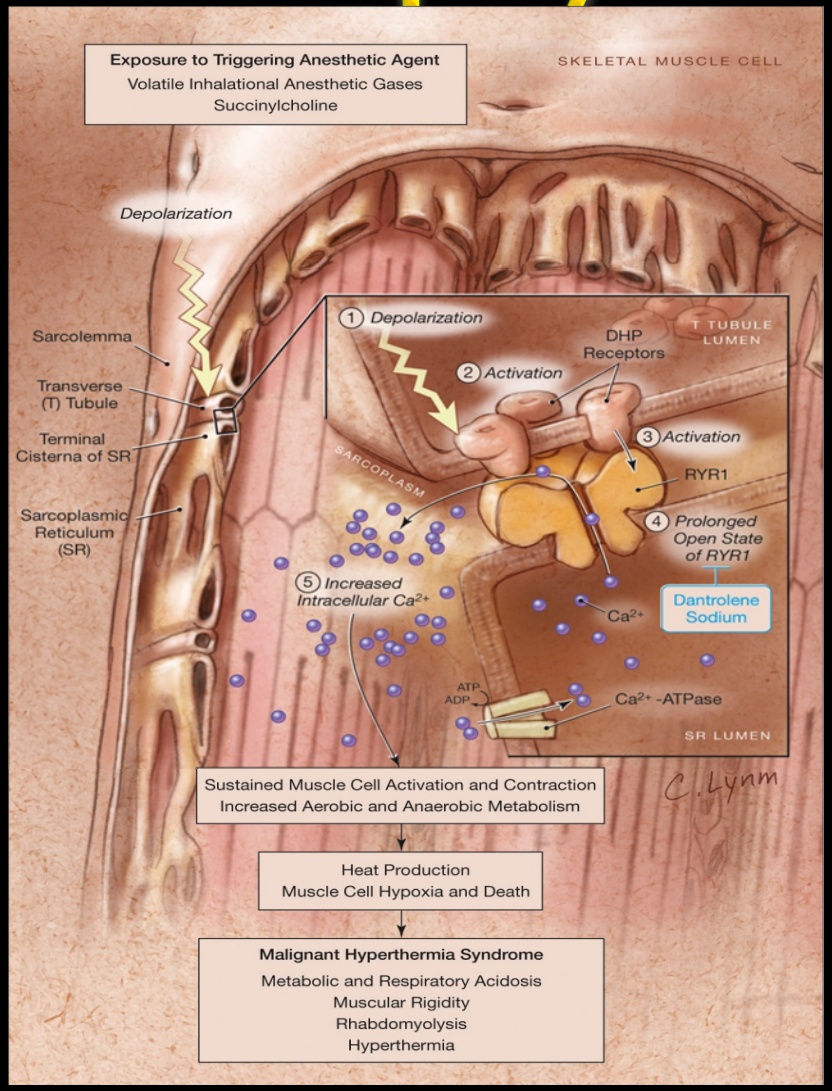




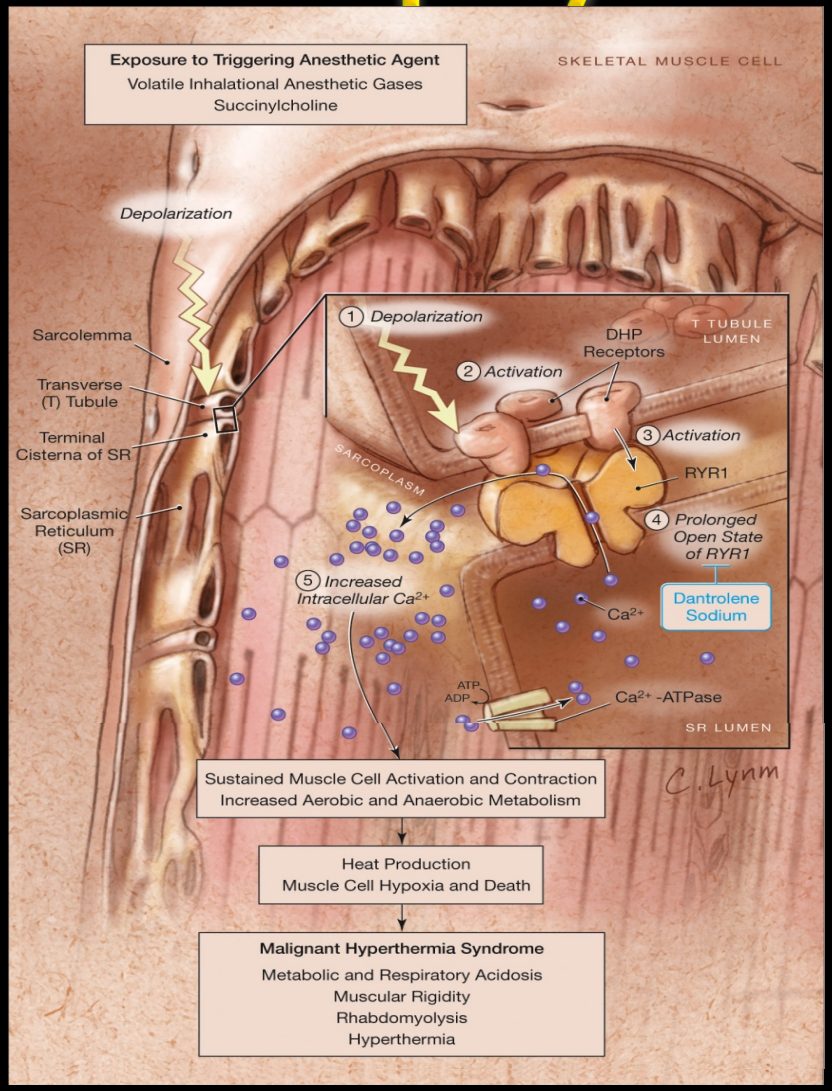
MH Pathophysiology



MH Pathophysiology



MH Pathophysiology



MH Mortality in ASC

Nearly all MH cases occur in normal people!

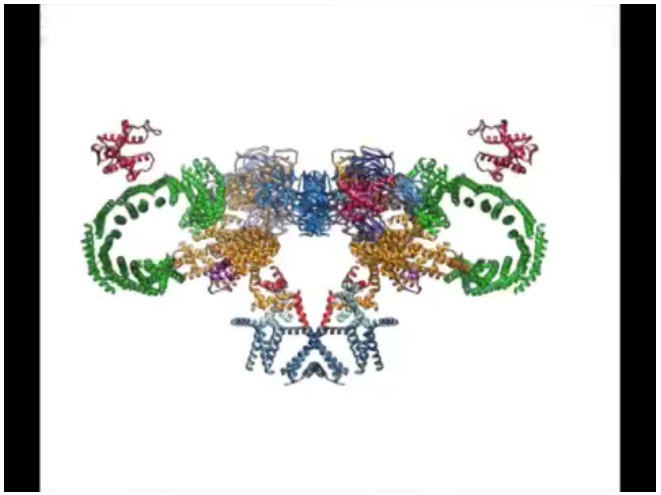
MH-Associated Diseases

3 categories

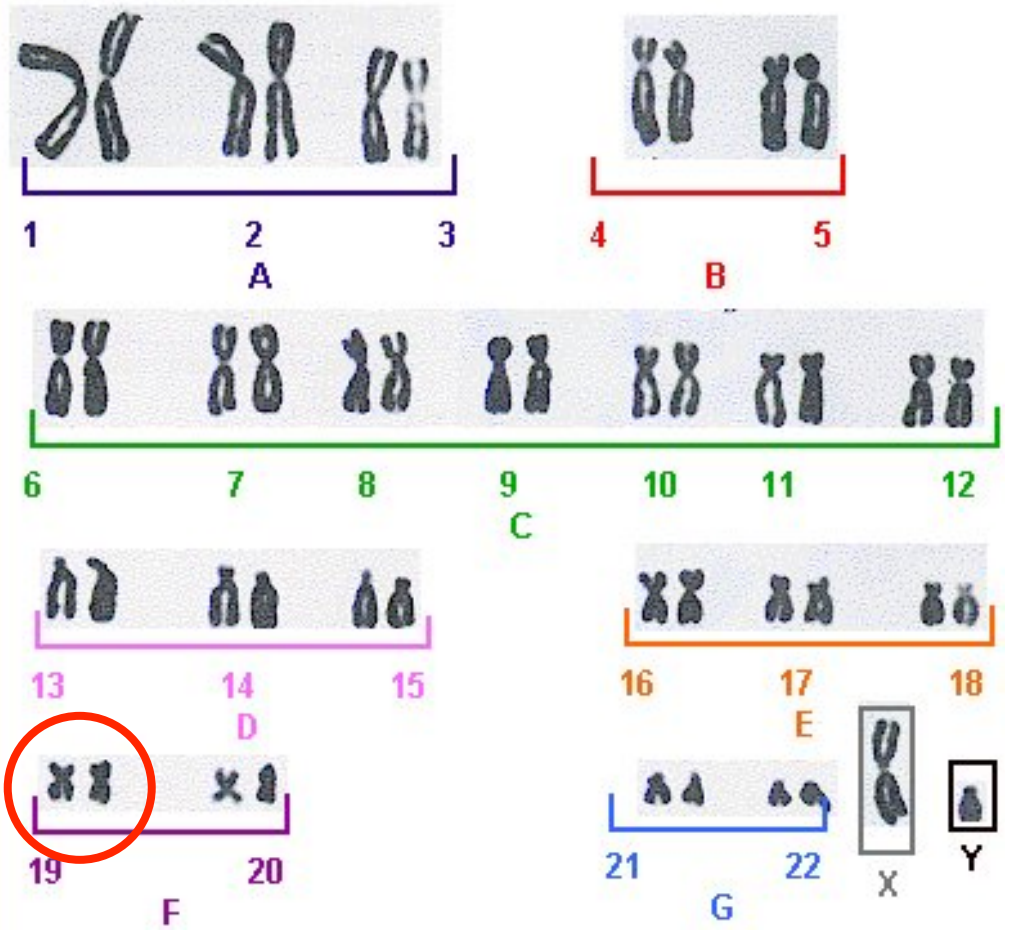
1. Definitely linked to MHS
2. Rhabdomyolysis but not MH
3. Unproven and unconvincing

Genetic Basis of MH

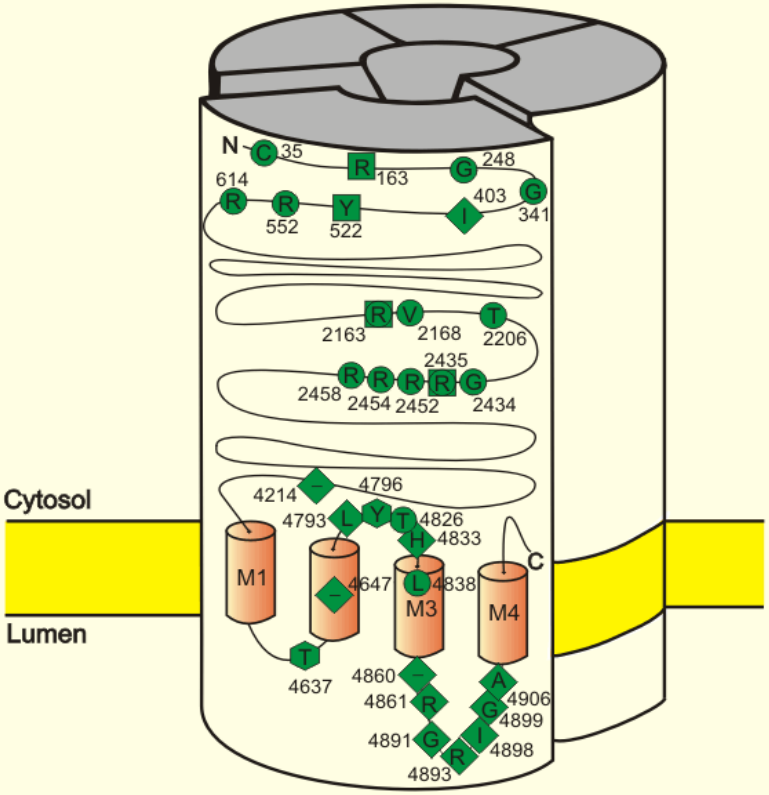
RYR 1



3D ryanodine from **Max Planck Society**



Ryanodine Receptor

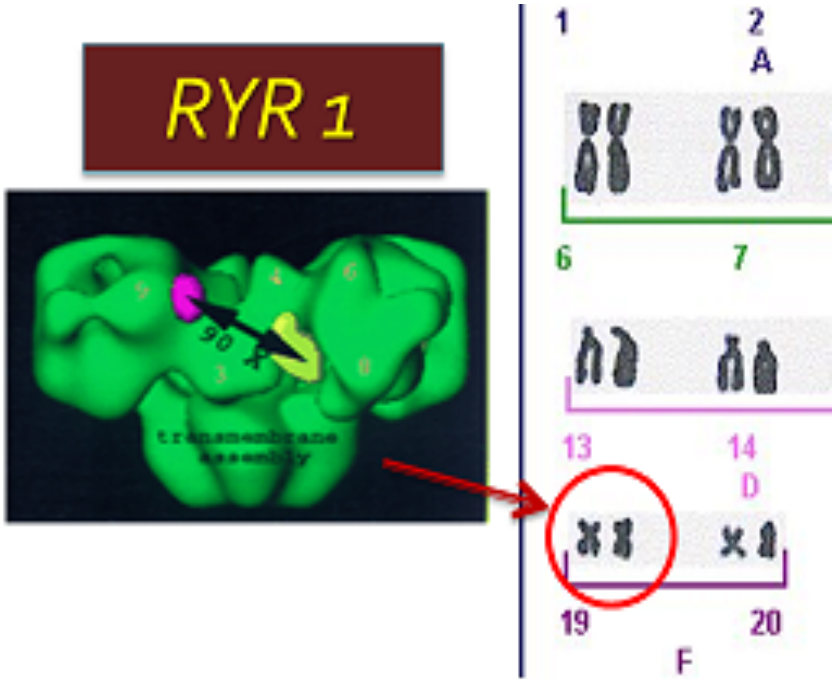


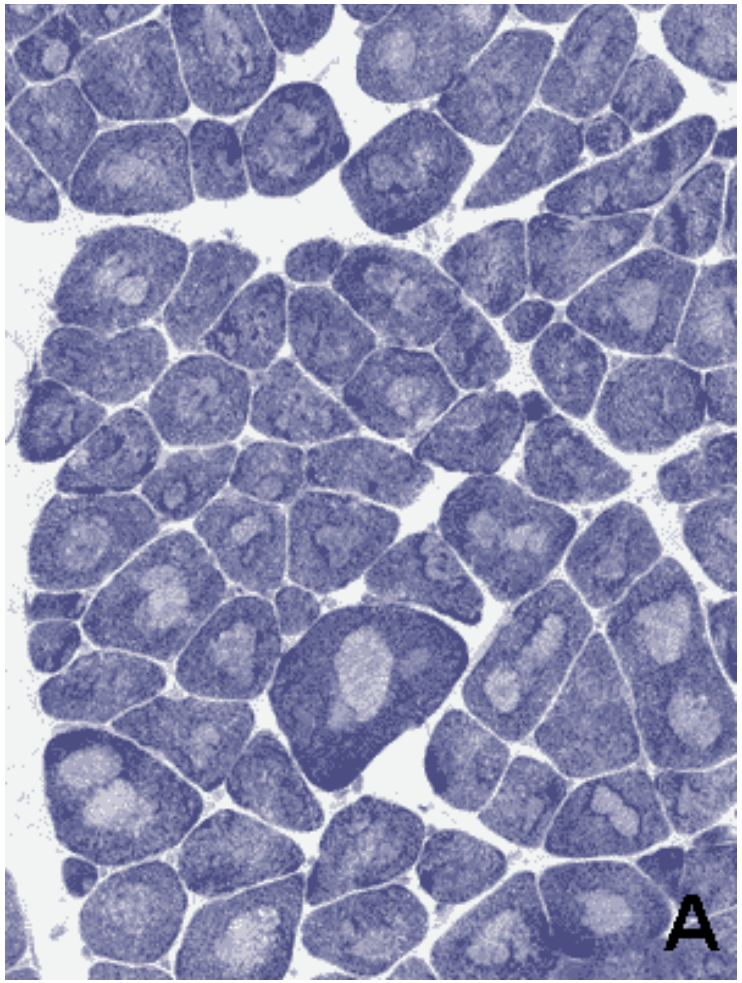
- malignant hyperthermia (MH)
- malignant hyperthermia/central cores (MH/CC)
- central core disease (CCD)
- central core disease with nemaline rods (CCD/n.rods)

– deletion

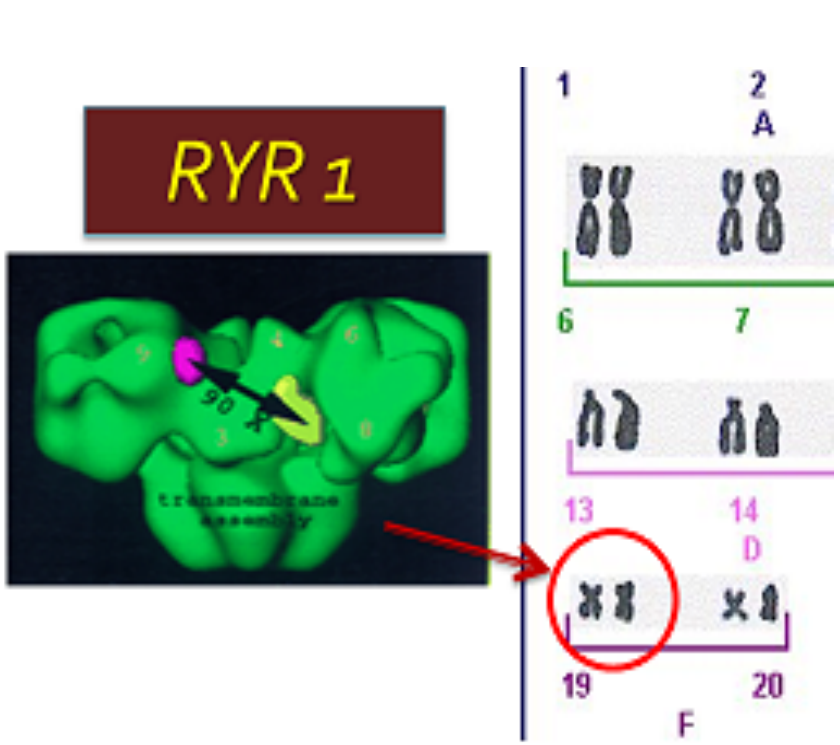
University of Ulm ryanofn.cdr 24.04.02 | Department of Applied Physiology

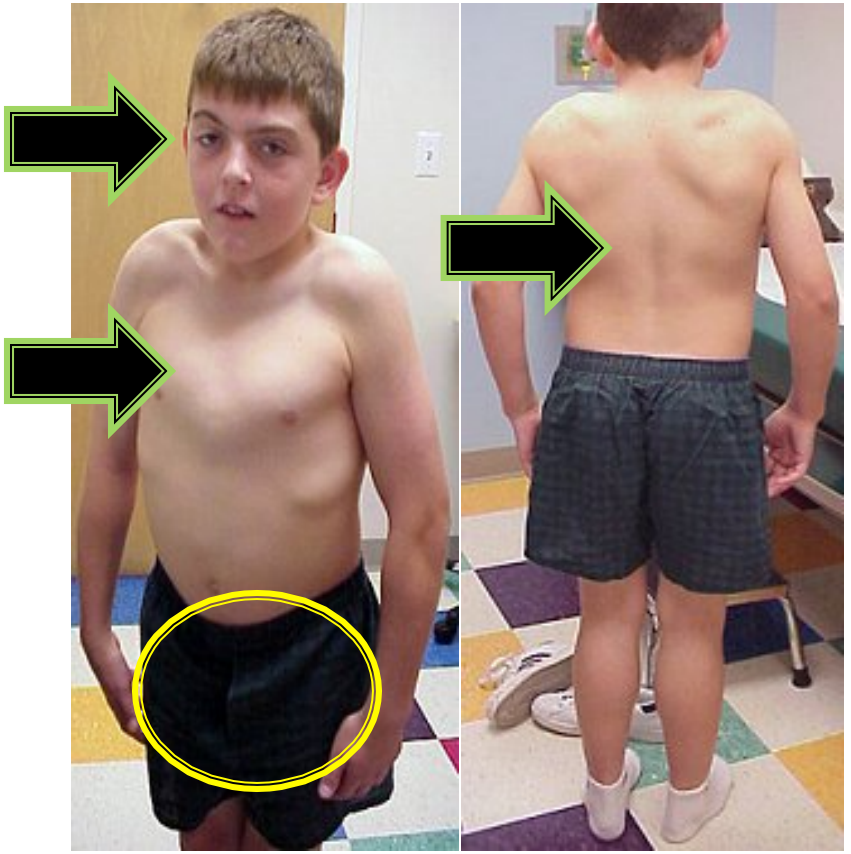
Central Core Myopathy





King-Denborough Syndrome





Obscure *RYR1* Myopathies

- MmD with external ophthalmoplegia
- Multiminicore myopathy
- Congenital myopathy w cores/rods
- Central nuclear myopathy
- NMD w uniform type 1 fibers
- Congenital fiber type disproportion

Native American Myopathy

STAC3

American Journal of Medical Genetics Part A 146A:1832–1841 (2008)

Clinical Report

Native American Myopathy:

Congenital Myopathy With Cleft Palate, Skeletal Anomalies, and Susceptibility to Malignant Hyperthermia

Demetra S. Stamm,[1,2] Arthur S. Aylsworth,[3,4] Jeffrey M. Stajich,[2] Stephen G. Kahler,[5] Leigh B. Thorne,[6] Marcy C. Speer,[2†] and Cynthia M. Powell[3,4*]

[1]Curriculum in Genetics and Molecular Biology, University of North Carolina, Chapel Hill, North Carolina
[2]Center for Human Genetics, Duke University, Durham, North Carolina
[3]Department of Pediatrics, Division of Genetics and Metabolism, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
[4]Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
[5]Department of Pediatrics, Section of Genetics, University of Arkansas for Medical Sciences, Little Rock, Arkansas
[6]Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Received 24 July 2007; Accepted 7 April 2008

Hypokalemic Periodic Paralysis

CACNL1A3

Am. J. Hum. Genet. 60:1316–1325, 1997

Malignant-Hyperthermia Susceptibility Is Associated with a Mutation of the α1-Subunit of the Human Dihydropyridine-Sensitive L-Type Voltage-Dependent Calcium-Channel Receptor in Skeletal Muscle

Nicole Monnier,[1] Vincent Procaccio,[1,3] Paul Stieglitz,[2] and Joël Lunardi[1,3]

[1]Laboratoire de Biochimie de l'ADN and [2]Département d'Anesthésie, CHU Grenoble, and [3]Laboratoire BECP, EA 2019 UJF, DBMS-CEA Grenoble, Grenoble

MH-Associated Diseases

3 categories

1. Definitely linked to MHS
2. Rhabdomyolysis but not MH
3. Unproven and unconvincing

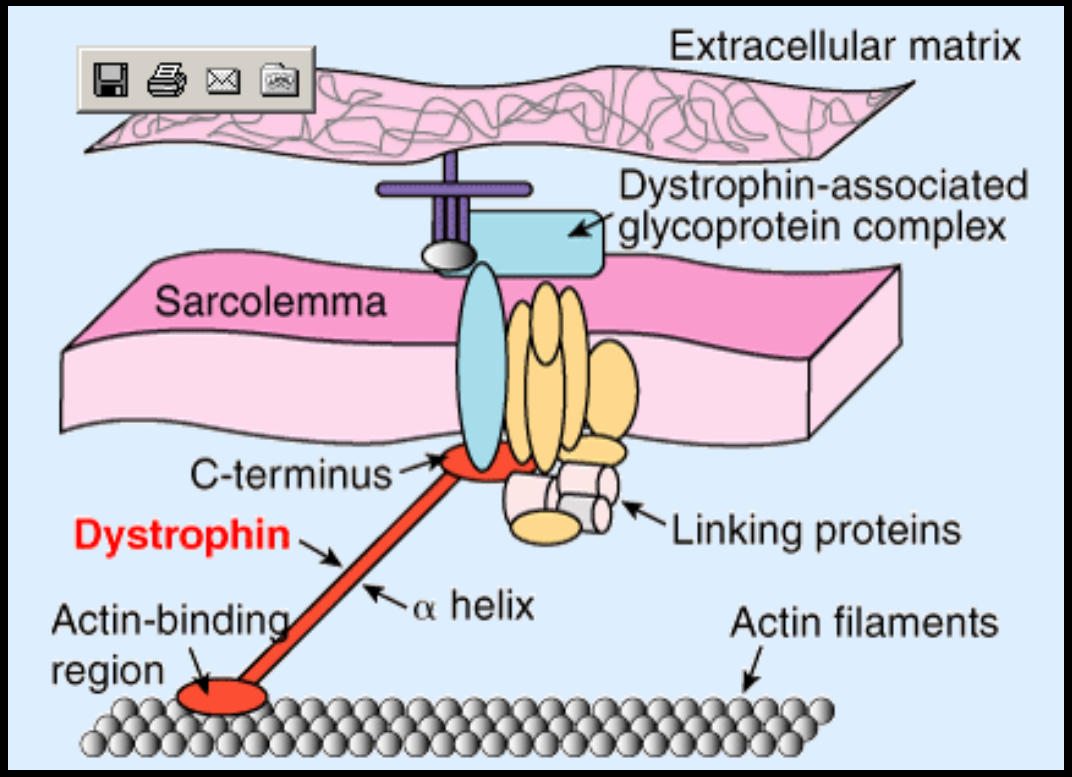
Rhabdomyolysis

- Muscular dystrophies
- McArdle's disease
- CPT-2 deficiency
- Myoadenylate deaminase deficiency

Muscular Dystrophies

- Duchenne type – X-linked
- Becker type – X-linked
- Limb-girdle
- Emery-Dreifuss
- Facioscapulohumeral
- Oculopharyngeal
- Congenital
- Myotonic

Duchenne Muscular Dystrophy



Duchenne Muscular Dystrophy

Recommendations:

- Succinylcholine absolutely contraindicated
- Volatile agents relatively contraindicated
- Pre-op screening

Duchenne Muscular Dystrophy

EndDuchenne.org

Parent Project Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE

UNDERSTAND DUCHENNE | CARE FOR DUCHENNE | ADVANCE RESEARCH | ADVOCATE | CONNECT | FUNDRAISE | DONATE NOW

Home / Care for Duchenne / Surgery and Anesthesia

Print Email

Care for Him
- Care Guidelines
- Explore by Area
- Explore by Stage
- Surgery & Anesthesia
- Emergency Care
- Resource Materials
- For Professionals

Surgery and Anesthesia

CONNECT

Email SIGN UP

HOW WE HELP

Heat Stroke and MH

- 12 year old child has acute MH in OR
- CHCT shows MH susceptibility
- 8 mos later: dies after football practice: T 108 F
- RYR-1 mutation detected in pt and relatives

Tobin et al. JAMA, 286, 2001

MH Susceptibility and Statin Myopathy

European Heart Journal Advance Access published February 18, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv043

REVIEW

Clinical update

Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management

Erik S. Stroes[1*], Paul D. Thompson[2], Alberto Corsini[3], Georgirene D. Vladutiu[4], Frederick J. Raal[5], Kausik K. Ray[6], Michael Roden[7], Evan Stein[8], Lale Tokgözoğlu[9], Børge G. Nordestgaard[10], Eric Bruckert[11], Guy De Backer[12], Ronald M. Krauss[13], Ulrich Laufs[14], Raul D. Santos[15], Robert A. Hegele[16], G. Kees Hovingh[17], Lawrence A. Leiter[18], Francois Mach[19], Winfried März[20], Connie B. Newman[21], Olov Wiklund[22], Terry A. Jacobson[23], Alberico L. Catapano[3], M. John Chapman[24], and Henry N. Ginsberg[25], European Atherosclerosis Society Consensus Panel[†]

MH Susceptibility and Statin Myopathy

Box 1 Risk factors for statin-associated muscle symptoms. Adapted from Mancini *et al.*[9]

Anthropometric	• Age >80 years old (general caution advised for age >75) • Female • Low body mass index • Asian descent
Concurrent conditions	• Acute infection • Hypothyroidism (untreated or undertreated) • Impaired renal (chronic kidney disease classification 3, 4, and 5) or hepatic function • Biliary tree obstruction • Organ transplant recipients • Severe trauma • Human immunodeficiency virus • Diabetes mellitus • Vitamin D deficiency
Surgery	• Surgery with high metabolic demands. The American Heart Association recommends temporary cessation of statins prior to major surgery[120]
Related history	• History of creatine kinase elevation, especially >10× the upper limit of the normal range • History of pre-existing/unexplained muscle/joint/tendon pain • Inflammatory or inherited metabolic, neuromuscular/muscle defects (e.g. McArdle disease, carnitine palmitoyl transferase II deficiency, myoadenylate deaminase deficiency, and malignant hyperthermia) • Previous statin-induced myotoxicity • History of myopathy while receiving another lipid-lowering therapy

Awake MH?

Identical *de novo* Mutation in the Type 1 Ryanodine Receptor Gene Associated with Fatal, Stress-induced Malignant Hyperthermia in Two Unrelated Families

Linda Groom, B.Sc.,* Sheila M. Muldoon, M.D.,† Zhen Zhi Tang, Ph.D.,‡
Barbara W. Brandom, M.D.,§ Munkhuu Bayarsaikhan, Ph.D.,‖ Saiid Bina, Ph.D.,#
Hee-Suk Lee, M.D.,** Xing Qiu, Ph.D.,†† Nyamkhishig Sambuughin, Ph.D.,‡‡
Robert T. Dirksen, Ph.D.§§

Anesthesiology 2011; 115:938

7 reported cases

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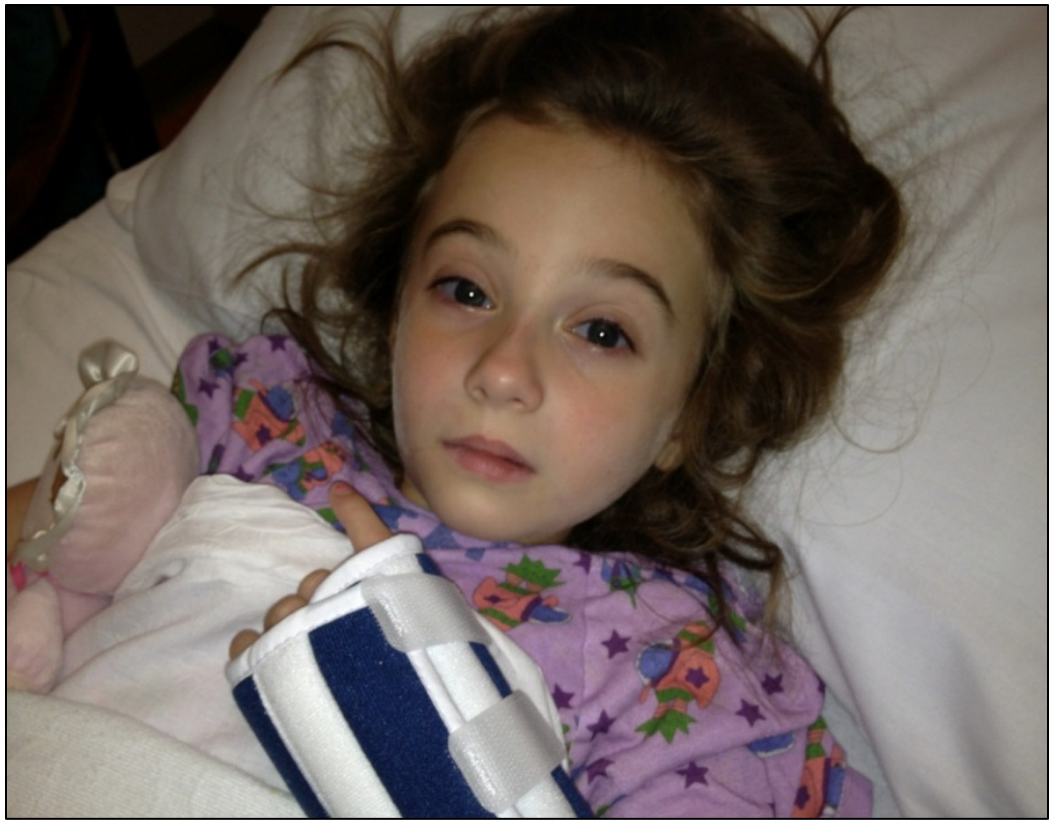
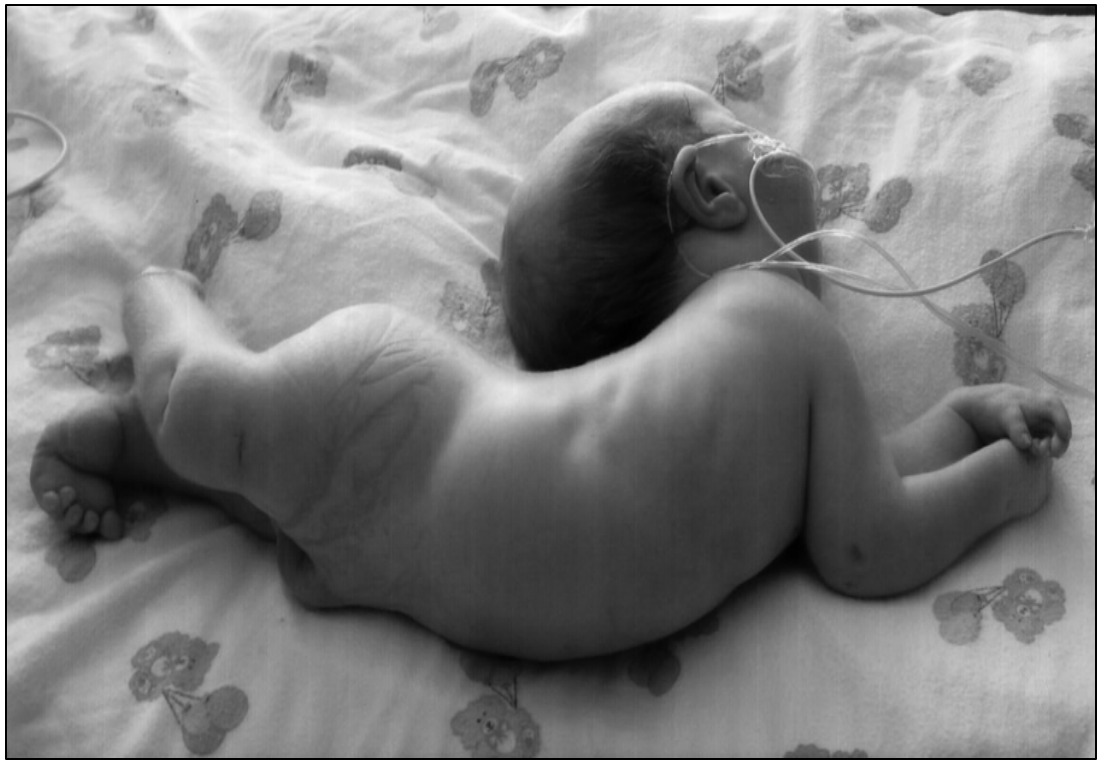
Noonan's Syndrome

Osteogenesis Imperfecta



Arthrogryposis



Mitochondrial Myopathies

- Kearns-Sayre syndrome (KSS)
- Leigh's syndrome
- Mitochondrial DNA depletion syndrome (MDS)
- Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)
- Myoclonus epilepsy with ragged red fibers (MERRF)
- Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
- Neuropathy, ataxia and retinitis pigmentosa (NARP)
- Pearson syndrome
- Progressive external ophthalmoplegia (PEO)

Mitochondrial Myopathies

No association with MH Susceptibility

Summary

Definitely associated with MH

- Centr
- Multi
- King-
- Any R
- Native American Myopathy
- Hypokalemic Periodic Paralysis

RYR1

Summary

Definitely associated with MH

- Centr
- Multi
- King-
- Any R
- Native American Myopathy
- Hypokalemic Periodic Paralysis

STAC3

Summary

Definitely associated with MH

- Central Core myopathy
- M
- K
- A
- Native American Myopathy
- Hypokalemic Periodic Paralysis

CACNL1A3

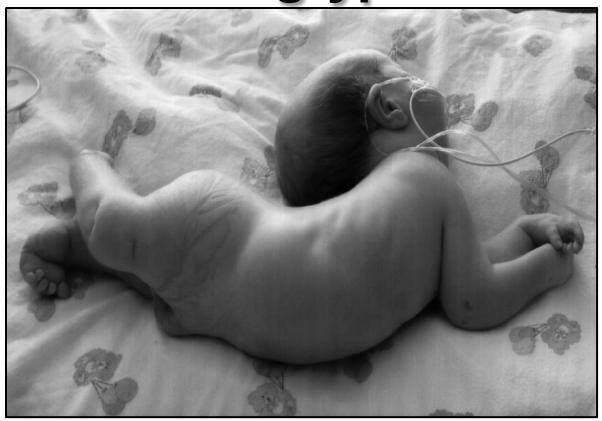
MH Susceptibility in Some Patients

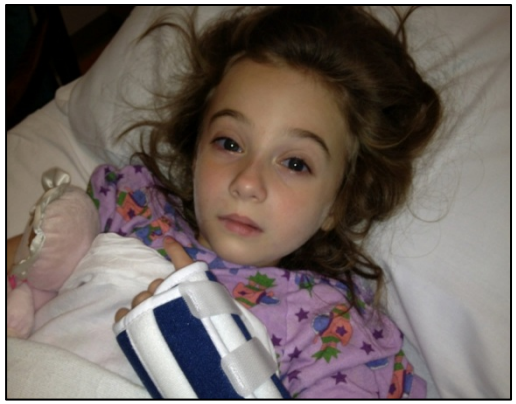
Heat Stroke rhabdomyolysis

Exercise-induced rhabdomyolysis

Diseases Not associated with MH Susceptibility

Arthrogryposis





O.I.

Noonan's

Duchenne's

Volatile Agent-induced Rhabdomyolysis

- Dystrophinopathies
- McArdle's disease
- Myoadenylate deaminase deficiency
- CPT-2 deficiency
- Exaggerated rhabdo after heat, exercise, or statins


STOP
To protect private
Patient Information
Only (1) family allowed at
the desk at a time
Last name appears on monitor
when prescription is ready
Thank You.

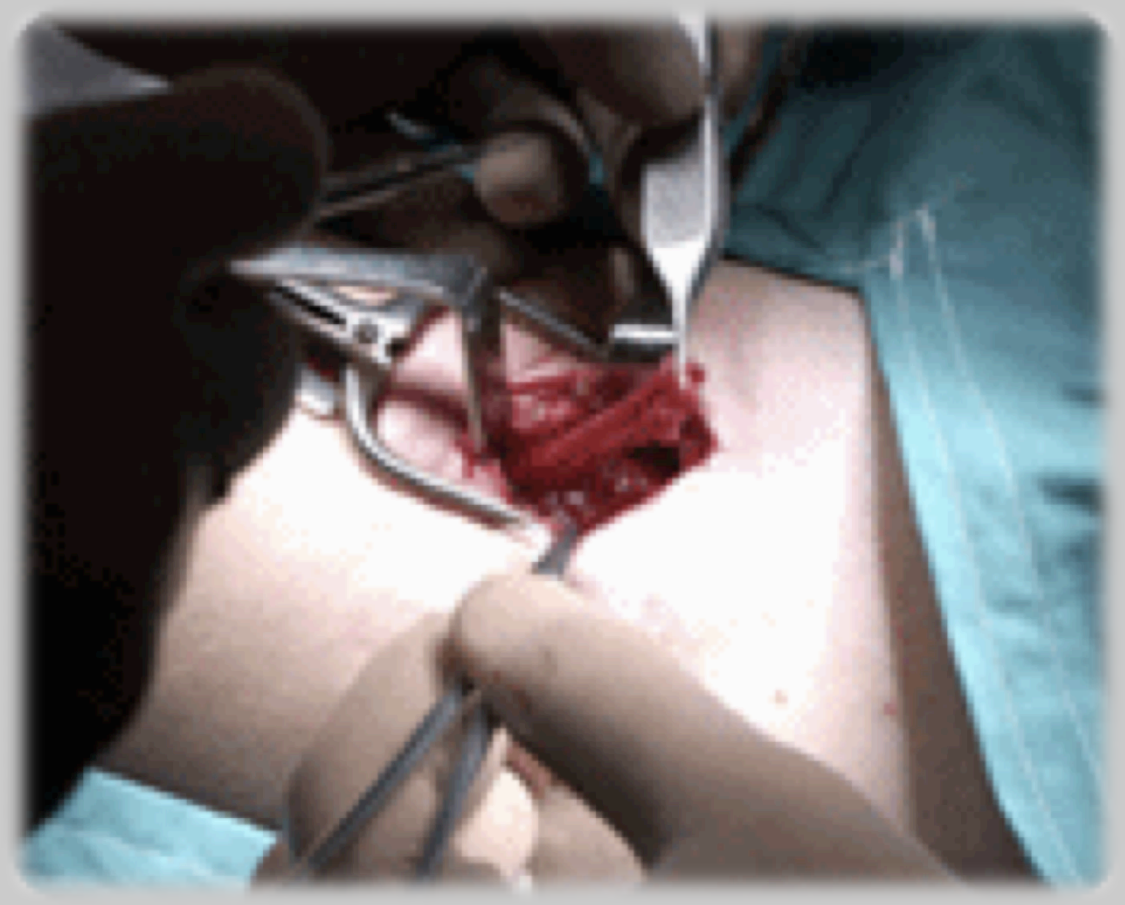
Malignant Hyperthermia Association of the United States

MHAUS GUIDELINES

Testing for Malignant Hyperthermia (MH) Susceptibility:

How do I counsel my patients?

Muscle Contracture Testing (CHCT)



CHCT Testing, U.S. and Canada

University of Minnesota
Minneapolis, MN
Paul A. Iaizzo, PhD
(612) 624-7912 or -3959

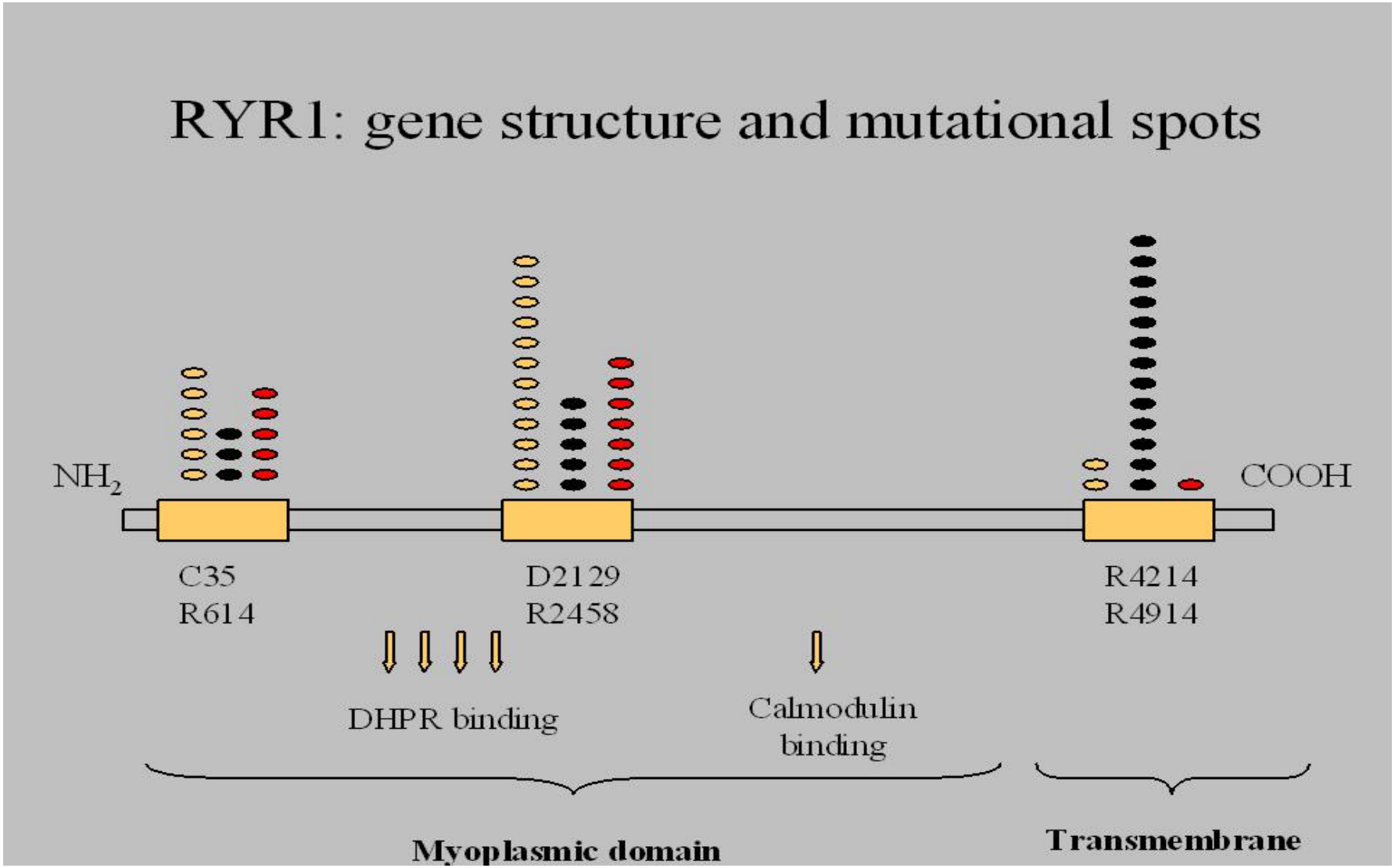
Uniformed Services University of the Health Sciences
Bethesda, MD
(Military & Civilian)
Sheila M. Muldoon, MD

University of California
Davis, CA
Timothy Tautz, MD

Wake Forest University
Winston-Salem, NC
Joseph R. Tobin, MD

Toronto General Hospital
Toronto, Ontario
Julian Loke, MD, FRCPC

Genetic Testing: RYR1 Gene Sequencing



PREVENTION GENETICS

DISEASE PREVENTION THROUGH GENETIC TESTING

MALIGNANT HYPERTHERMIA SUSCEPTIBILITY NEXTGEN SEQUENCING (NGS) PANEL

TEST METHODS

NEXTGEN SEQUENCING

Test Number	Test	Price	CPT Code(s)
1383	NextGen Sequencing (3 genes)	$1,590	81479 (x2), 81408

In addition, Targeted Familial Mutation testing via Sanger sequencing is available for any gene in the panel:

Test Number	Test	Price	CPT Code
100	Targeted Familial Mutations - Single Exon Sequencing	$250	81479
200	Targeted Familial Mutations - Double Exon Sequencing	$370	81479
300	Targeted Familial Mutations - Triple Exon Sequencing	$440	81479

WWW.MHAUS.ORG

BASICS OF PEDIATRIC ANESTHESIA

MH-Related Diseases

Who Really Needs a Non-triggering Technique?

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litmanr@email.chop.edu